IN THE DRAWINGS

Please add one new drawing (Fig. 11), as attached hereto on a sheet labeled "NEW SHEET" in the top margin in accordance with under 37 C.F.R. §1.121(d).

REMARKS

Amendments in the specification

Tables 1–4 in Examples 3, 4, 6 and 7 are amended to insert data which were unintentionally omitted from the English-language specification submitted on February 4, 2004. Applicant filed the present application with a German-language specification on July 29, 2003 and timely submitted an English translation thereof on February 4, 2004. The data now inserted were present in the originally-filed German-language specification and therefore do not constitute new matter.

Furthermore, the present application validly claims priority of German application No. DE 102 34 673 filed on July 30, 2002, which contains the same tables with the data. By virtue of this priority claim, therefore, the present amendment of Tables 1–4 does not constitute new matter.

New paragraph **[0001]** is added to provide cross-reference to applications from which the present application claims priority.

New paragraph **[0025]** is added to refer to Fig. 11, which by the present amendment replaces a diagram formerly inserted in the text.

Opportunity has been taken, in amending the specification and claims, to correct typographical errors in the specification and to re-phrase where it has been desirable to do so for enhanced clarity, conciseness and antecedent basis, or to better conform to standard U.S. specification-drafting practice, for example in recitation of Markush groups. Initial capitalization of the word "rotigotine" has been removed throughout (except where the word starts a sentence or is used in a heading) to avoid any possible inference that the word is being used as a trademark. Spelling of the chemical name of rotigotine has been corrected throughout.

Amendments in the claims

Following amendment as requested herein, Claims 1–16, 18 and 20–25 are pending in the present application. Claims 17 and 19 are canceled and new Claims 24 and 25 are added by the present amendment. No increase in total claim number or in number of independent claims results from this amendment. No additional claim fees are believed payable.

Paragraph numbers below refer to the Substitute Specification (clean copy) attached hereto.

Claims 17 and 19 are canceled without prejudice as being similar in scope to Claims 49 and 57 respectively of copending application Serial No. 10/523,908. Depending on the eventual disposition and possible future amendment of the '908 application, Applicant may elect to reintroduce subject matter of Claims 17 and 19 to the present application to the extent such subject matter is not barred by statutory double patenting.

Claims 1–16, 18 and 20–23 are amended to better conform to U.S. claim-drafting standards. For example, where appropriate the indefinite article is inserted at the beginning of each independent claim, and the definite article at the beginning of each dependent claim. The transition phrase "wherein" replaces nonstandard transition phrases such "characterized in that" or "for which". The transition phrase "comprises" or "comprising" replaces "contains" or "containing". Initial capitalization of the word "rotigotine" has been removed throughout to avoid any possible inference that the word is being used as a trademark.

All multiple dependency is removed by the present amendment. In general, dependent claims are amended to depend from the broadest claim providing antecedent basis; it will be understood that such amendments are made without prejudice to possible later amendment as to dependency.

Claim 3 is amended to recite that the hot-meltable adhesive comprises an amine-resistant silicone adhesive and, in mixture therewith, at least one softener, in place of the previous recitation that the hot-meltable adhesive consists of a mixture of an amine-resistant silicone adhesive and at least one softener. This broadens the scope of the claim by permitting optional additional components of the hot-meltable adhesive. Support for the open "comprises" transitional phrase is found in the specification, for example at paragraph **[0043]**, in particular the disclosure therein of a "hot-meltable adhesive containing a suitable mixture of a silicone-based adhesive and at least one softener."

Claims 3, 10 and 13 are amended to recite "pharmaceutically acceptable" in place of "suitable" with respect to softeners. Support for "pharmaceutically acceptable softeners" is found in the specification, for example at paragraph **[0076]**.

Claim 9 is amended to recite rotigotine in "free-base" form. The previous recitation of

"biocatalytic" base in Claim 9 is believed to arise from mistranslation of the original German-language application. Support for rotigotine in free-base form is found in the specification, for example at paragraph **[0058]**.

Claims 10, 12 and 13 are amended by insertion of a period (.) at the end of each claim.

Claim 14 is amended from independent to dependent form, so as to incorporate the limitations of Claim 1 from which it now depends. Claim 14 is further amended to delete from the preamble the redundant phrase "for the continuous transdermal administration of rotigotine"; this phrase will be seen to be a non-limiting descriptor of a purpose or utility of the TTS defined by the body of the claim.

Claim 20 is amended to clarify that it is the components of the cement matrix "other than the rotigotine" that are pre-melted, as will be clear from the process step reciting that the rotigotine is introduced to the pre-melted matrix.

New Claims 24 and 25 contain similar recitations to Claims 21 and 23 respectively, except that they depend from Claim 18 instead of Claim 20. Prior to the present amendment, Claims 21 and 23 were multiply dependent *inter alia* from Claims 18 and 20; thus addition of Claims 24 and 25 does not represent new matter.

Amendments in the drawings

Fig. 11 is added as a new drawing. The diagram now provided as Fig. 11 is found in the originally-filed German-language specification dated July 29, 2003 and in the German priority document as "Diagram 1" within the text description of Example 9, but inadvertently omitted in the English-language translation filed on February 4, 2004. Therefore, Fig. 11 does not constitute new matter.

No new matter is added by any amendment of specification, claims or drawings herein, and no change in inventorship results from any amendment of the claims herein.

RESPONSE TO OFFICE ACTION DATED OCTOBER 5, 2007

1. Obviousness-type double patenting

Claims 1–23 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly unpatentable over Claims 28–59 of copending application Serial No. 10/523,908.

The rejection is provisional because the allegedly conflicting claims have not yet been patented. Applicant may elect to argue to overcome this ground of rejection or to provide a terminal disclaimer (to the extent necessary) once the present claims have been found to be otherwise allowable and/or once the co-pending application issues as a patent. As noted above, Claims 17 and 19 are cancelled by the present amendment and the present rejection is moot with respect to these claims.

2. Objection under 37 C.F.R. §1.75(c)

Claims 5–10, 16, 17 and 21–23 are objected to for improper multiple dependency. By amendment herein, Claim 17 is canceled and all multiple dependency in remaining claims has been removed. Therefore, the present objection is now moot and withdrawal of the objection is respectfully requested.

Claims 10–13 are objected to for absence of a period (.) at the end of each claim. By amendment herein, a period (.) is added to the end of each of Claims 10, 12 and 13. Claim 11 appears to already have a period. Therefore, the present objection is now moot and withdrawal of the objection is respectfully requested.

3. Rejection under 35 U.S.C. §112, first paragraph

Claims 14 and 15 are rejected under 35 U.S.C. §112, first paragraph as allegedly not enabling for the release profiles recited.

By amendment herein, Claim 14 (and Claim 15 dependent thereon) is amended to depend from and incorporate the structural limitations of Claim 1. As the level of skill in the art is very high (as admitted in the present Action, page 5), one of skill in the art can without undue experimentation, using standard pharmacokinetic protocols, test any TTS falling within the scope of Claim 1 and determine whether it meets the functional limitations of Claims 14 and 15 (0.4–2 ng/ml average plasma concentration over a 5-day or 7-day period respectively).

Furthermore, specific TTS's are described in the specification that meet these functional limitations; one of skill in the art can without undue experimentation prepare these TTS's and confirm the plasma levels attainable by their application, and can modify these TTS's and test the modified TTS's in order to determine whether they retain the plasma level properties shown.

Withdrawal of the present rejection under 35 U.S.C. §112, first paragraph is respectfully requested.

4. Rejection under 35 U.S.C. §112, second paragraph

Claim 20 is rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. By amendment herein Claim 20 is recast as a method-to-make (process) claim. Applicant believes the present ground of rejection is now moot and respectfully requests withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

5. Rejection under 35 U.S.C. §101

Claim 20 is rejected under 35 U.S.C. §101 because its recitation of a "use" results in an improper process claim. By amendment herein Claim 20 is recast as a method-to-make (process) claim. Applicant believes the present ground of rejection is now moot and respectfully requests withdrawal of the rejection under 35 U.S.C. §101.

6. Rejection under 35 U.S.C. §103(a)

Claims 1–4, 11–15 and 18–20 are rejected under 35 U.S.C. §103(a) as allegedly obvious over U.S. Patent No. 5,807,570 ("Chen"), in view of Metman *et al.* (2001) Clin. Neuropharmacol. 24:163–169 ("Metman") and U.S. Patent No. RE 36,754 ("Noel"). This rejection is respectfully traversed for reasons detailed below.

6.1. No apparent reason to combine the elements in the fashion claimed

The disclosure of Chen is directed to methods, pharmaceutical formulations and systems for transdermal administration of certain indolone derivatives such as ropinirole. As indicated in the present Action, the Chen systems contain neither (1) rotigotine nor (2) a hot-meltable adhesive. However, the Examiner argues that it would have been obvious to a person of ordinary skill to modify the Chen system to include rotigotine as an active agent and a hot-meltable silicone adhesive incorporating an organic wax, based on the teachings of Metman and Noel, respectively. Applicant respectfully disagrees with this argument, at least because there was no motivation at the time of the present invention for one of ordinary skill to select the particular elements identified by the Examiner from Chen, Metman and Noel to construct a TTS as now claimed.

For a finding of obviousness based on a combination of documents, there must be an apparent reason for a skilled artisan to make the alleged combination. *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007) (establishment of obviousness includes determining "whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"), emphasis added. Moreover, in seeking to establish obviousness, a combination of references cannot be constructed by using Applicant's disclosure. As stated by the court in *ATD Corporation v. Lydall, Inc.*, 159 F.3d 534, 48 USPQ2d 1321, 1329 (Fed. Cir. 1998) (emphasis added):

> Determination of obviousness can not be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention. There must be a teaching or suggestion within the prior art, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources of information, to select particular elements, and to combine them in the way they were combined by the inventor.

Chen does not teach or suggest a transdermal system in which the active agent is dispersed and at least partly dissolved in a hot-meltable adhesive, as required by the present claims. Even if it were possible (and Chen provides no guidance on this point) to prepare such a system with ropinirole, it does not follow that such a system could be prepared using rotigotine as the active ingredient.

Metman merely discusses transdermal administration of rotigotine, stating that "the data suggest that rotigotine CDS is an effective treatment for advanced Parkinson's disease and permits patients to substantially lower L-dopa doses without loss of antiparkinsonian efficacy," without expanding on the structure and composition of the TTS used or of any TTS that might be used. Furthermore, even if rotigotine (based on Metman) were an obvious replacement for ropinirole in Chen's system (which is not admitted herein), there remains no motivation to modify Chen to provide a hot-meltable adhesive and then to combine Chen and Metman in the fashion now claimed, as required under *KSR v. Teleflex*.

Turning now to Noel, that disclosure relates *inter alia* to a hot-melt pressure-sensitive silicone adhesive composition containing organic waxes, and to use of such a composition in a matrix-type transdermal drug delivery device. Noel provides no disclosure as to

compatibility of a wax-containing silicone adhesive composition with any active ingredient, or to solubility of any active ingredient in such a composition, thus motivation is lacking to extract the silicone/wax component from Noel and combine it with rotigotine in the fashion now claimed.

In summary, no apparent reason existed for one of ordinary skill in the art to select and extract specific elements from the three separate references applied in the present rejection and combine these elements to construct a TTS of the present invention, as required under *KSR v. Teleflex*. Such selection, extraction and combination can be made only in hindsight, and is therefore non-obvious under *ATD v. Lydall*.

6.2. No reasonable expectation of success

The standard for determining obviousness has recently been clarified by the U.S. Supreme Court in *KSR v. Teleflex, supra*: "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results"; "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art" (emphasis added).

Without admission that the Chen, Metman and Noel references are combinable, Applicant submits that one of ordinary skill could not have had reasonable expectation of success in preparing a TTS having rotigotine dispersed in a hot-melt adhesive, at least because rotigotine is sensitive to oxidation. The oxidation issue is well addressed in the present specification, at paragraphs **[0026]**–**[0027]**:

> It was surprising to find that rotigotine lends itself superbly to processing by the hot-melt method, that it remains stable under short-term heating to temperatures up to at least 160°C, that it can be homogeneously worked into matrices produced by the hot-melt process, and that it is released from the hot-melt matrices in continuous fashion and at a therapeutically desirable rate.
>
> In particular, the inventors were surprised to find that the rotigotine, being susceptible to oxidation, remains stable in the hot-melt process even when heated to temperatures around 160°C. While at higher temperatures in an oxygen-containing atmosphere, rotigotine tends to decompose in oxidative fashion, it is amazingly stable in the hot adhesive melt and is present in the

> matrix at a purity level that is routinely better than 98% and generally over 99% ...

In brief, one of ordinary skill would not have reasonably expected that use of a hot-melt process would be workable, due to sensitivity of rotigotine to oxidative decomposition.

Furthermore, any influence of inclusion of organic wax in a hot-melt adhesive composition on release properties of rotigotine would not have been predictable to one of ordinary skill. In particular, it could not have been predicted that inclusion of a wax would not only provide rheological benefit in preparing the hot-melt TTS but would controllably retard release, making it possible to provide a TTS for administration over a period of 5–7 days. See, for example, the present specification at paragraphs **[0049]–[0051]**:

> A surprising discovery showed that adding wax, especially organic wax such as ceresine or ozokerite, also has an effect on the *in-vitro* murine-skin permeation of rotigotine from the hot-melt silicone TTS. As is evident from FIG. 2, rotigotine's permeation rate decreases as the wax concentration increases ...
>
> This property of the wax is significant especially for developing a TTS designed for application over several days, for instance 7 days. That type of multi-day patch requires a high infusion of rotigotine, which poses the risk of an excessive release of rotigotine at the beginning of the application phase ("dose dumping") ...
>
> Apart from the surprising discovery that the wax content in the matrix serves to retard the release of the active substance, varying the wax content will not only modify the dynamic viscosity of the adhesive but additionally offers the equally surprising option of regulating the active-substance release.

The predictability of results required for a showing of obviousness under the *KSR v. Teleflex* standard is therefore absent.

Withdrawal of the present rejection under 35 U.S.C. §103(a) is respectfully requested.

7. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated or rendered moot herein. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Action and that the application is in condition for allowance.

If personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number below.

Respectfully submitted,

HARNESS, DICKEY & PIERCE, P.L.C.

James C. Forbes

James C. Forbes
Agent for Applicant
Reg. No. 39,457
Tel. 847-412-6350

Attachments
Copy of Request for Correction of Filing Date
Substitute Specification (mark-up version)
Substitute Specification (clean version)
New Sheet containing drawing (Fig. 11)